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In This Issue

Clinical Analysis of Adverse Drug Reactions

Introduction

Adverse drug reactions (ADRs) represent an important public health problem. Despite efforts to reduce the incidence of medication-related adverse events, morbidity and mortality from drug-induced disease continue to be unacceptably high. Furthermore, methods for ADR detection, evaluation, and monitoring remain inadequate. While some ADRs are idiosyncratic and unpredictable, others can be anticipated based on knowledge of a medication's clinical pharmacology. In fact, an estimated 30% to 60% of ADRs may be preventable (1–5).

Regrettably, adverse reactions to medications are generally not well studied, and the mechanisms of some remain poorly described. The problem is further exacerbated by the inadequate training that clinicians receive in the basic principles of applied pharmacology and therapeutics. This article will focus on the clinical detection of ADRs and on factors that may increase ADR risk.

Epidemiology

Although some adverse drug reactions are minor and resolve without sequelae, others can cause permanent disability or death. ADRs occur commonly, but estimates of incidence vary considerably. This is due to substantial under reporting of ADRs and differences in study methodology, populations studied, and ADR definitions. Adverse drug reactions account for 2.9% to 15.4% of all hospital admissions in the United States (6, 7). The incidence may be highest in the elderly and other compromised populations. Nearly 16% of nursing home residents are hospitalized because of an ADR (8). A significant risk factor for hospitalization is the concomitant use of 7 or more medications. ADRs are believed to be the fourth to sixth leading cause of death among hospitalized patients (1). A recent study suggests that an estimated 6.7% of hospitalized patients experience serious adverse drug reactions (defined as those requiring or prolonging hospitalization, are permanently disabling, or result in death) (1). Of 1133 drug-related adverse events reported in a study of more than 30,000 medical records, 19.4% were attributable to an adverse drug reaction (4). The incidence of ADRs in hospitalized HIV-infected patients was reported to be 20% (9). Up to 30% of patients may experience an ADR while hospitalized, of which 3% may be life-threatening, and most receive an average of nine drugs per hospitalization (10). Adverse drug reactions have been reported to increase the length of hospital stay by 2.2 to 4.6 days and to increase hospital costs by more than $2500 per event (11). The economic burden of ADRs has been estimated to be in the billions of dollars annually (12).

Definitions

An adverse drug event is any undesirable experience associated with the use of a medical product in a patient (13). This broad definition includes adverse drug reactions and other events (including medication errors) related to the prescribing, preparation, dispensing, or administration of medications. Karch and Lasagna (14) defined an ADR as any response to a drug that is noxious and unintended and that occurs at doses used in man for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose. The World Health Organization (WHO) adopted a slightly modified version of this definition. According to WHO, an ADR is any response to a drug which is noxious

and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function (15). Both definitions are limited to reactions caused by medications and purposely exclude therapeutic failures, overdose, drug abuse, noncompliance, and medication errors. The U.S. Food and Drug Administration (FDA) defines an ADR as any undesirable experience associated with the use of a medical product in a patient (16). The FDA defines serious reactions as those that are life-threatening; require intervention to prevent permanent injury; or result in death, initial or prolonged hospitalization, disability, or congenital anomaly.

Classification

Adverse drug reactions can be classified simply according to their onset or severity. ADRs are occasionally classified as acute, sub-acute, or latent. Acute events are those observed within 60 minutes after the administration of a medication and include anaphylactic shock, severe bronchoconstriction, and nausea or vomiting (17). Sub-acute reactions occur within 1 to 24 hours and include maculopapular rash, serum sickness, allergic vasculitis, and antibiotic-associated diarrhea or colitis. Latent reactions require 2 or more days to become apparent and include eczematous eruptions, organ toxicity, and tardive dyskinesia.

ADRs can also be classified as mild, moderate, or severe. Mild reactions, such as dysguesia associated with clarithromycin, are bothersome but may not require a change in therapy. Moderate reactions, such as amphotericin B-induced hypokalemia, often require a change in therapy, additional treatment, or continued hospitalization. Reactions that are disabling or life-threatening, or those that considerably prolong hospitalization, are classified as severe (18).

The classification of Rawlins and Thompson is perhaps the most widely used to describe adverse drug reactions (19). Although this classification system continues to evolve, it serves a useful purpose. Adverse reactions are categorized as Type A or B. Type A reactions are those that extend directly from a drug's pharmacological effects. They are often predictable and dose-dependent and may account for up to two-thirds of all ADRs. Type A reactions also include adverse effects resulting from drug overdose and drug-drug interactions. Sedation caused by an antihistamine or hypotension caused by a beta-adrenergic antagonist are considered Type A reactions. Type B reactions are idiosyncratic or immunologic reactions that are often rare and unpredictable. Examples of Type B reactions include aplastic anemia caused by chloramphenicol or rash induced by beta-lactam antibiotics. Albeit not universally accepted, other authors have extended this classification system to include Types C, D, and E reactions to describe "chemical," delayed, and end-of-treatment reactions, respectively.

Gell and Coombs (20) developed a classification system (Types I through IV) to describe immune-mediated hypersensitivity reactions to medications. Immune system components such as intact skin, phagocytes, and complement act as constant barriers to foreign invasion. Lymphocytic and antibody activity are increased after repeated exposure to antigens. Drug molecules or metabolites act as antigens and induce the production of antibodies. Antibodies are produced if lymphocytes are able to recognize the antigenic determinants of foreign particles. Drugs may cause more than one of the four types of hypersensitivity reactions in this classification scheme. For example, reactions to penicillins can be classified under more than one type based on their clinical presentation and associated laboratory findings.

Type I reactions are IgE-mediated and cause manifestations of allergic symptoms due to the release of immune mediators such as histamine or leukotrienes. They typically occur within minutes of drug exposure and may manifest as generalized pruritus, urticaria, angioedema, anaphylaxis, rhinitis, or conjunctivitis (21). Anaphylaxis can result from exposure to any antigen (e.g., penicillin) and may be fatal in the absence of prompt medical intervention.

Type II reactions involve cytotoxic antibodies (IgG- or IgM-mediated) which react with antigens on the cell surface; the combination then causes cell damage due to the presence of neutrophils and monocytes or complement-induced cell lysis. Examples of Type II reactions are the hemolytic anemias caused by methyldopa or quinine. Acute graft rejection is another Type II hypersensitivity reaction.

Type III reactions are caused by tissue injury due to immune complexes. The antigen-antibody complexes are usually cleared by the immune system; however, repeated contact with antigens can cause the complex to deposit in tissue and result in tissue injury. Serum sickness is the classic example of a Type III reaction. Medications associated with serum sickness include many antibiotics, phenytoin, salicylates, barbiturates, non-steroidal anti-inflammatory drugs, isoniazid, antisera, hydralazine, captopril, and sulfonamides. Procainamide-induced lupus is also considered a Type III reaction.

Type IV reactions occur when T-cells bind to a specific antigen, thereby causing the release of cytokines. The onset of these reactions may be delayed by more than 12 hours. Topical application of drugs may result in allergic contact dermatitis and photosensitivity. These reactions typically manifest initially as a skin rash but may become systemic upon subsequent exposure to the antigen.

Clinical Detection of ADRs

Adverse reactions can result from the use of drugs, diagnostic agents, biologicals (including vaccines), nutrients, fluids, electrolytes, and complementary or alternative products. Adverse effects may be attributable to the parent compound, a metabolite, a pharmaceutical excipient, or even a component of the drug delivery system. Occasionally, more than one agent may be involved. Adverse drug reactions, whether expected or not, occur with nearly all medications and have been observed regardless of route or mode of administration.

Some ADRs are caused by most or all medications in a class, while others are agent specific. Nausea, vomiting, and diarrhea have been observed with most antibiotics, yet only chloramphenicol and certain sulfonamide antibiotics have

been consistently implicated as causes of aplastic anemia. Some pharmacological effects such as sedation from an antihistamine may be considered adverse effects when they are not intended, but desired effects when they are prescribed specifically for an indication for which they may be beneficial (e.g., sleeping aid). Several body systems are commonly affected by ADRs and few are spared. Adverse effects range from nonspecific symptoms to organ-specific toxicity that can be confirmed objectively. Certain medications are widely recognized for selectively targeting specific organs or body systems. For example, the aminoglycoside antibiotics are known to cause nephrotoxicity and ototoxicity; most antineoplastics produce predictable bone marrow suppression, and bleomycin and bulsulfan cause pulmonary fibrosis.

Herbal products have been identified as a source of serious adverse reactions and interactions (22). Since the passage of the Dietary Supplements Health and Education Act of 1994 (DSHEA), the use of herbal and dietary supplements has increased dramatically in the United States. Drug metabolites also have been implicated in the pathogenesis of some adverse drug reactions.

Pharmaceutical excipients and drug delivery systems have been associated with severe allergic and nonallergic adverse reactions (23–25). Excipients are pharmacologically inert substances that include binders, fillers, coloring agents, buffers, lubricants, detergents, emulsifiers, flavors, solvents, adsorbants, aerosol propellants, stabilizers, and sweeteners. Some of the adverse effects are mild and self-limiting. Lactose in some products may be associated with gastrointestinal complaints and diarrhea in lactose-intolerant patients. Sorbitol-containing liquid preparations can also cause diarrhea. Examples of excipients found to cause morbidity or mortality include the sulfite preservatives, the coloring agent tartrazine, and the polyoxyethylated castor oils (Cremophor®) used as emulsifiers in parenteral products. Para-amino benzoic acid (PABA) and PABA derivatives have been associated with severe allergic reactions. The first major drug-related tragedy in U.S. history was caused by the solvent diethylene glycol found in a formulation of the oral antibiotic sulfanilamide. Exposure to this substance resulted in more than 100 deaths and led to passage of the Food and Drug Act of 1937. Occasionally, even drug formulations themselves have been reported to cause adverse effects. Gastrointestinal irritation, bezoars, and intestinal obstruction have been reported as a result of drug formulations that do not disintegrate or dissolve properly.

Components of drug delivery systems have also been associated with severe reactions. Reports of latex allergy continue to increase as more health care workers are exposed to medical devices that contain this substance, including protective gloves. Incidence of latex sensitization ranges from 1% to 6% of the general population and about 8% to 12% of continuously exposed health care workers (26,27). Leaching of the plasticizer, di-2-ethylhexylphthalate (DEHP), from intravenous drug delivery systems has also been associated with toxicity, particularly in susceptible individuals exposed for long periods.

Risk Factors

Since many adverse reactions are predictable, recognition and understanding of potential risk factors may be the most critical steps in ADR prevention. Table 1 lists the primary ADR risk factors.

Table 1. ADR Risk Factors

- Concurrent use of multiple medications
- Multiple co-morbid conditions
- Drug dose and duration of exposure
- Extremes of age (neonates, children, and elderly)
- Female sex
- Genetic predisposition
- Prior history of drug reactions and hypersensitivity
- End-organ dysfunction
- Altered physiology
- Inappropriate medication prescribing, use, or monitoring
- Lack of patient education and other system failures

Concurrent use of multiple medications is another major ADR risk factor. The potential for clinically significant drug interactions and additive adverse effects increases as the number of medications in a regimen increase (28,29). In a study of over 9,000 hospital admissions, the strongest predictor of ADRs was the large number of concurrent prescription medications (OR=2.94) (30). Irrational prescribing, inappropriate use, or insufficient monitoring of medications can predispose to adverse outcomes. To minimize the incidence of adverse reactions, each medication must have a clear indication, and specific therapeutic and toxic endpoints should be established prior to the start of treatment. Factors that contribute to polypharmacy include increasing age, multiple medical conditions, over prescribing, multiple medical providers, absence of a primary care provider, use of multiple pharmacies, frequent drug regimen changes, hoarding of medications, and self-treatment (31). Polypharmacy is of particular concern in the elderly because they are already susceptible to ADRs. Elderly patients often suffer disproportionately from various acute and chronic illnesses and are likely to require more medications (31). They are also more likely than their younger counterparts to have impaired CNS function and not adhere to the prescribed regimen. Elderly patients in the community use an average of three prescription and nonprescription medications, while those in nursing homes receive an average of five to eight prescription drugs at the same time (32). Patient education and ongoing medication regimen review can minimize the problem of polypharmacy.

The presence of multiple co-morbid conditions (e.g., diabetes, asthma, congestive heart failure, obesity) further increases the risk of ADRs. Such patients may have altered physiology and some degree of end-organ dysfunction (e.g., renal, hepatic, cardiovascular, pulmonary). Conditions such as renal dysfunction may not be readily apparent in the elderly or in those with muscle wasting or malnutrition.

The extent and duration of drug exposure can also predispose to toxicity. This is particularly true for patients with end-organ dysfunction. An estimated 70% to 80% of adverse drug reactions may be dose related (33). Not surprisingly, the medications most commonly associated with adverse reactions are those with narrow therapeutic indices such as digoxin, warfarin, heparin, theophylline, aminoglycosides, and anticonvulsants (34).

Age may be an important risk factor for the development of ADRs, and young children and the elderly may be particularly vulnerable. Despite this risk, documentation of ADRs in these groups is poor, and adverse reactions are often attributed to non-drug causes. Moreover, there is often inadequate experience with medications in these populations because they are often excluded from clinical trials (35).

The incidence of ADRs increases with increasing age (30). In addition to the increased risk posed by polypharmacy and co-morbid conditions, there are important age-related changes in the pharmacokinetic disposition of a number of medications in the elderly. While drug absorption is least likely to be affected, drug distribution, metabolism, and elimination are often altered (36). Age-related decreases in renal function are probably most important. However, changes in body composition, particularly the relative increase in adipose tissue that occurs with aging, may increase the distribution volume of lipid soluble medications, thereby prolonging their half-life and altering peak and trough plasma concentrations. For example, the increased distribution volume of benzodiazepines in elderly patients results in lowered peak and raised trough plasma concentrations after a dose of these drugs. The net effect in the elderly is that these drugs have a reduced efficacy in inducing sleep and an exacerbated posthypnotic hangover effect. Pharmacodynamic changes may also be affected by age but are not consistently predictable. In general, elderly patients may be more sensitive to the effects of many medications and often require lower initial dosages (32).

Children of all ages also may be particularly susceptible to adverse drug reactions. In a surveillance study of over 10,000 pediatric admissions to several hospitals, 0.2% of admissions to the neonatal intensive care unit were caused by ADRs (37). Twenty-two percent of children with cancer were hospitalized as a result of ADRs. Among all other pediatric admissions studied, 2% were possibly or probably due to ADRs. The drugs most frequently implicated were phenobarbital, aspirin, phenytoin, ampicillin or amoxicillin, theophylline or aminophylline, trimethoprim-sulfamethoxazole, and diphtheria-pertussis-tetanus vaccine. Dosages of some medications begun in childhood (e.g., antiasthmatics, antiepileptics, stimulants, and insulin) may require careful adjustment during adolescence to minimize the risk of ADRs (40). Changes in body weight, drug distribution, and drug clearance can influence drug disposition and affect dosing.

Neonates are especially vulnerable to ADRs because they are sometimes exposed to drugs before birth and have immature renal and hepatic drug clearance capacities. Additionally, there is insufficient information on the clinical pharmacology of various drugs in this age group to guide rational pharmacotherapy (38, 39).

Women appear to be at greater risk for ADRs than men (41-43). Data from the Glaxo Wellcome-Sunnybrook Drug Safety Clinic gathered over a 10-year period suggest that women over 18 years of age experience more ADRs than their age-matched male counterparts (44). More than 77% of all ADRs, including those classified as severe, were reported in women. A recent cohort study evaluating the adverse-event experience with 48 newly marketed drugs in the United Kingdom revealed an incidence per 10,000 patients of 12.9 ADRs in males and 20.6 in females (42). Females over the age of 19 were 43% to 69% more likely to experience a suspected ADR. Sex differences in pharmacokinetics and pharmacodynamics, differences in circulating hormone concentrations, and more frequent use of medications which inhibit hepatic metabolism are all cited as possible explanations for the observed differences (43). Women may also use more medications and are more likely to report adverse effects (43). Historically, women have been under represented in clinical trials, but this imbalance is reversing as regulations on their participation have changed (41).

Race and ethnicity may also be risk factors for ADRs. Prior personal or family history of ADRs may be predictive of future adverse reactions. Genetic polymorphisms for many metabolic reactions have been well documented (45). Prescribing some medications without regard to genetic differences in metabolism can result in therapeutic failures or drug toxicity (45,46). For example, differences in acetylator phenotype can alter the metabolism of some drugs and influence the risk of certain adverse reactions. Slow acetylators, for example, may be more likely than rapid acetylators to develop hepatotoxicity from isoniazid treatment.

Genetic differences can also influence the likelihood of some drug interactions. For example, co-administration of the antiarrhythmic propafenone to patients being treated with metoprolol substantially reduces metoprolol metabolic clearance in extensive CYP2D6 metabolizers, thereby resulting in exaggerated ß-adrenoreceptor blockade and possibly precipitating congestive heart failure, nightmares, and blurred vision. This interaction essentially converts extensive CYP2D6 metabolizers to poor metabolizers, a phenomenon termed phenocopying, but does not impair metoprolol metabolism in poor metabolizers (45,47).

Detection Methods

ADRs are sometimes not recognized and often go unreported. In fact, the principal limitation of ADR detection methods is the lack of awareness of what constitutes an ADR. Most ADRs are brought to medical attention by subjective reports and patient complaints. Linkage of a drug with an ADR is most often suspected on the basis of temporal association, but more objective confirmatory evidence often is lacking. Additionally, there are perceived barriers

to reporting ADRs, and some clinicians fear that reporting suspected ADRs may expose them to liability. Moreover, many clinicians often fail to attribute new signs or symptoms, or changes in laboratory tests or diagnostic studies to drug therapy. Medications should be carefully screened and systematically ruled out as possible causes of any abnormal finding on physical examination or from laboratory tests or diagnostic procedures

Given the perceived failure of spontaneous reporting systems and the paucity of ADR reports, some institutions have instituted more active methods of ADR detection to supplement spontaneous reports. Medication order screening has become a common practice in U.S. hospitals. Manual chart reviews and audits and computer programs are used for retrospective, concurrent, and prospective medication utilization evaluation. Certain events often prompt an evaluation of a suspected adverse reaction. These include abrupt discontinuation of a medication, abrupt dosage reduction, orders for antidotes and emergency medications, orders for special tests or serum drug concentrations, and abnormal results from laboratory tests and medical procedures.

Spontaneous reports to the FDA and drug manufacturers, post-marketing surveillance, and data from ongoing observational studies and clinical trials provide other means for detecting important ADRs that may have not been detected during drug development.

Clinical Evaluation

Clinical evaluation of adverse drug reactions requires careful assessment of the patient and evaluation of pertinent factors. The patient's clinical status and severity of the reaction should be determined promptly in order to fully characterize the event and plan the optimal initial course of action. After obtaining a detailed description of the event, a differential diagnosis can be formulated that considers alternative etiologies. Alternative explanations for the adverse findings (e.g, non-drug causes, exacerbation of pre-existing condition, laboratory error) should be carefully evaluated, based on the characteristics of all clinical signs and symptoms. These include severity, extent, temporal factors (onset, duration, frequency), presence of palliative or provoking factors, quality (character or intensity), response to treatment, and other associated findings.

A medical history (including a systematic review of body systems) and a physical examination should be obtained, along with relevant laboratory tests and diagnostic procedures. Relevant patient factors should be noted, including age, race, ethnicity, sex, height, weight, and body composition. Concurrent medical conditions or other factors should be considered that may cause, aggravate, or even mask or confound the manifestations of the reaction. These include conditions such as dehydration, autoimmune disorders, end-organ dysfunction, malnutrition, HIV infection, or pregnancy. Recent invasive medical procedures, treatments (e.g., dialysis), or surgery and any resultant complications (e.g., hypotension, shock, infection) should also be noted. Exposure to contrast material, radiation, or environmental or occupational hazards, and use of tobacco, caffeine, alcohol, and illicit substances should be investigated.

Because of the importance of drug interactions, a detailed medication history should be recorded that identifies all prescription, non-prescription, and alternative or complementary medications used by the patient. In addition to medication dosage, other factors that may contribute to the development of adverse reactions include medication administration route, method, site, schedule, rate, and duration. A history of allergies, intolerances, and other medication reactions should be fully investigated. The potential for cross-allergenicity or cross-reactivity should not be overlooked. The possibility of drug-induced laboratory test interference (analytical or physiological) and drug-drug or drug-nutrient interactions should also be explored.

Management of specific adverse reactions is beyond the scope of this article. However, it is intuitive that the offending agent should be discontinued if the event is life-threatening or intolerable to the patient, especially when a reasonable alternative exists (48). Palliative and supportive care (e.g., hydration, glucocorticoids, or compresses) may be necessary for management of some adverse reactions. In some cases, specific reversal agents or antidotes are also needed (e.g., flumazenil for benzodiazepines, naloxone for opioids, and protamine for heparin). Some medications should not be stopped abruptly, and gradual dosage reduction may obviate rebound effects or other complications. In some circumstances, re-challenge with the suspected medication or desensitization may be warranted. Because some adverse reactions are delayed or may have an unpredictable course, careful monitoring and re-evaluation are essential.

Causality Assessment

It is often challenging to establish a cause-and-effect relationship between a drug and a specific adverse reaction. This is especially true when appropriate ADR information is incomplete, inconsistent, or altogether lacking. Additional confounding factors include co-administration of other medications, non-drug variables, and concurrent illnesses.

Several methods used to determine causality have been described and compared (49–52). The Naranjo algorithm is perhaps the most commonly accepted causality assessment instrument (53). Most methods of causality evaluation emphasize reproducibility and validity of the data. Reproducibility depends on the precision of the instrument and thereby affects its reliability. Lack of reproducibility results from random error. Reproducibility is achieved when inter- and intra-observer variability are small, or when agreement between observations is high (54,55). Validity is the extent to which a test accurately measures what it was designed to measure. Lack of validity most often results from experimental error. Validity of a test can be evaluated by measuring its sensitivity and specificity. This is difficult to establish when a

gold standard is absent—as is often the case in ADR assessment (54,55). Causality assessment instruments attempt to quantify information about adverse drug reactions and determine the probability that an ADR was caused by a specific medication. The presence of some or all of the elements listed in Table 2 increases the probability of drug culpability in association with an ADR.

Table 2. Clinical Evidence Suggestive of Causality

- Temporal relationship
- Positive de-challenge
- Positive re-challenge
- Dose-response relationship
- Biological plausibility
- Absence of alternative etiologies
- Objective confirmation
- Prior reports of reaction
- Past history of reaction to same or related medication

A chronological or temporal relationship between the administration of a drug and the development of an adverse reaction is essential for establishing causality. Time-to-onset of reaction must be plausibly related to the administration of the drug. However, because some reactions may not appear for weeks or months after the start of therapy with a medication, they may be erroneously implicated as the cause of the reaction. The presence or absence of alternative etiologies and confounding variables also must be investigated (49,56). A history of the reaction in a patient receiving the same drug or a similar compound increases the possibility that the association may be causal, and prior reports of similar reactions lend credibility to a cause-and-effect relationship. The absence of prior reports decreases the likelihood but does not eliminate the possibility that the reaction is due to the medication in question. If a precedent cannot be found, the plausibility of the reaction should be based on a consideration of the known clinical pharmacology of the drug (56). Further evidence to support an assertion of drug culpability requires objective data such as abnormally high serum drug concentrations, specific physical examination findings, or other laboratory or diagnostic data characteristic of a drug reaction.

A positive de-challenge (i.e., when a reaction resolves after a drug is discontinued or a specific antagonist is administered) suggests that the medication may be culpable. A positive re-challenge (i.e., when signs or symptoms of the reaction recur after the drug is re-administered), provides even more convincing evidence linking the drug to the reaction but may not be ethically permissible and clinically justifiable. In any case, re-challenge should be done only after de-challenge is complete and signs and symptoms of the reaction have completely abated (57). The probability of a cause-and-effect relationship is further strengthened if the reaction worsens when a higher dose of the medication is administered. To further evaluate the probability of a drug-induced effect, Naranjo (58) suggests that a placebo challenge be considered.

Reporting Requirements

Documentation and reporting of adverse events are critical steps in the effort to prevent ADRs. Adverse reactions should be clearly described and documented in the medical record. This is mandated by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) as a method for preventing serious adverse reactions from re-exposure to a medication to which a patient may be allergic or intolerant. Most adverse reactions, however, are not properly documented or reported. Despite the importance of spontaneous adverse drug reaction reporting, it is estimated that only 1 in 10 serious adverse drug reactions is reported to the Food and Drug Administration (FDA). Given the large number of drug prescriptions written each year in the United States, this figure most likely over-estimates the number of reports.

The reason most often cited for the lack of adverse event reporting is uncertainty about the causality of an adverse reaction. While confirmation of an ADR is ideal, it is often not feasible. The FDA readily acknowledges this limitation and continues to encourage the reporting of all *suspected* adverse drug reactions through its MedWatch program. Detailed instructions for reporting adverse events associated with drugs, medical devices, vaccines, and veterinary products can be found at the following URL: *http://www.fda.gov/medwatch/report/hcp.htm*. The FDA is particularly interested in receiving reports of adverse reactions involving new chemical entities and serious reactions involving any medical product.

Adverse drug reaction data are largely drawn from spontaneous reports to the FDA or pharmaceutical manufacturers, post-marketing surveillance studies, and published case reports or case series. These sources are critical for identifying ADRs that are not detected or clearly characterized during pre-registration clinical trials. ADRs are least likely to be detected when they have a low incidence, when drug exposure is minimal or infrequent, when the ADR manifestation or effect has a high background frequency (e.g., common symptom due to causes other than the medication), and when a time or dose relationship are weak or absent (59).

Pharmaceutical manufacturers are required to report serious adverse drug events to the FDA within 15 days of receiving a report. All other reports are submitted on a quarterly basis for the first three years after marketing, and annually thereafter. Reports of serious adverse reactions, either during clinical trials or after drug marketing, occasionally result in FDA-mandated inclusion of so-called "black box" warnings in the product label. These warnings usually are drug-specific, but occasionally pertain to an entire pharmacological class of medications. New data relating to drug safety and efficacy also sometimes prompt

the FDA to require pharmaceutical manufacturers to disseminate "dear doctor" letters to alert health care providers of findings that have the potential for substantial impact on public health. These and other safety notifications can be accessed at the following URL: *http://www.fda.gov/medwatch/safety.htm.*

ADR Detection in Clinical Trials

Methodology

Detection of adverse reactions during clinical trials requires careful and systematic evaluation of study participants before, during, and after drug exposure. Objective data must be gathered to determine that study subjects meet all inclusion criteria and do not have any conditions that preclude their participation. Standard laboratory and diagnostic tests are used to establish patients' baseline health and functional status. Such tests should be appropriate for the drug and condition under investigation and should be conducted at predetermined intervals. Typically, serum chemistries and renal, hepatic, hematologic, electrolyte and mineral panels are included. A complete medical history (including a review of all body systems) and physical examination and a complete medication history (including allergies and intolerances) should be included. Use of prescription, nonprescription, and alternative and complementary medications by study participants specifically should be documented.

Study protocols should clearly outline how adverse events will be detected, managed, and reported. Study data should be entered on case report forms designed for the study, and a quality control mechanism for ensuring the accuracy and integrity of the data should be established prior to the start of data collection. Computerized record keeping (i.e., electronic case report forms) can facilitate audits, data management, and data analysis. Adverse drug event questionnaires using extensive checklists of symptoms organized by body system have been developed for use in clinical trials (60). These are typically administered at baseline and at predetermined intervals during and after a study. To increase their utility and allow for comparisons between treatment groups, the questionnaires should be administered by a blinded investigator. Since healthy individuals who are free of illness and not taking medications can occasionally experience symptoms similar to those reported as drug side effects, adequate controls must be used in studies examining adverse drug reactions (61). Comprehensive questionnaires increase the likelihood that patient interviews are conducted in a consistent and non-superficial manner. Moreover, they minimize the risk of bias (particularly from focusing on known adverse effects) and can be useful for inter- and intra-subject comparisons. Of course, study participants should be encouraged to report all serious, unexpected, or bothersome symptoms, especially those that persist or require some treatment or intervention.

Toxicity criteria developed by the World Health Organization (WHO) and the National Cancer Institute (NCI) provide guidelines for objectively and systematically categorizing adverse effects according to type and severity grade. NCI's Common Toxicity Criteria (CTC) are particularly useful for studies involving antineoplastic drugs but are equally applicable to other drug categories. The CTC organizes related adverse events alphabetically according to body system or disease. For example, the "endocrine" category includes specific adverse effects such as gynecomastia and hypothyroidism. Specific criteria are detailed for grading the severity of each adverse effect. The CTC can be accessed at the following URL: *http://ctep.info.nih.gov/CTC3/default.htm.*

Limitations

Despite attempts to screen candidate drugs during the early stages of preclinical development and identify all serious adverse effects during the course of pre-registration clinical trials, some drugs are approved for marketing that later are found to pose unacceptable public health risks. This is not altogether surprising given the limitations of subject enrollment and duration of therapy during the clinical development of new drugs. Given these and other constraints, rare and unusual ADRs often cannot be detected before marketing approval is granted. Uncommon adverse reactions (e.g., those affecting 0.2% of patients or fewer) frequently will not be detected during clinical development (51). For example, it has been estimated that 3000 patients at risk must be studied in order to have 95% certainty in detecting an ADR with an incidence of 1/1000 (62). Given that most drugs are approved despite limited experience in human subjects, a drug such as chloramphenicol, that causes aplastic anemia with an incidence of 1 in 20,000 or less, would likely be approved today without realizing its potential to induce blood dyscrasias.

Even under optimal conditions, some ADRs will not be detected because drug exposure may be limited (i.e., short-term studies). Also, some latent ADRs may go undetected because of superficial monitoring or insufficient follow-up. Occasionally, ADRs may not be detected readily because they manifest slowly and exhibit symptoms that closely resemble those of the underlying condition for which the drug was being used. An example of this is the severe mitochondrial damage and subsequent hepatic injury induced by the synthetic nucleoside analogue, fialuridine (FIAU), which was being investigated for the treatment of hepatitis B infection (63).

Not only are study participants too few in number to detect uncommon ADRs, but typically they are not representative of the population at large that is likely be exposed to the medication in routine clinical use. Many studies have traditionally excluded children, the elderly, women of childbearing age, and patients with severe forms of the target disease. Moreover, patients with multiple co-morbidities and those taking potentially interacting medications are often not included. It is, therefore, not surprising that even well designed and impeccably conducted studies yield results that often are not generalizable.

Reporting Requirements

All experimental studies involving human subjects require the approval of an institutional review board (IRB) and ongoing review of study progress. The IRB is specifically charged with the responsibility of safeguarding the rights and welfare of human research subjects. In many cases, the study is monitored by a data and safety monitoring board (DSMB) in cooperation with the IRB. The DSMB reviews all reports of adverse reactions and conducts interim analyses of the data to ensure that study participants are not subjected to excessive risks or denied treatment with an effective medication if one arm of a study is found to be superior to another. Drugs being studied under an investigational new drug application (IND) must conform to criteria set forth by the FDA. Under these criteria, all adverse events must be promptly reported to the FDA, the IRB, and the drug sponsor. Serious adverse events (as defined earlier in this article) must be reported within 15 calendar days—7 days if they are life-threatening or result in death. This reporting requirement cannot be waived even if causality (relationship of the event to the research) has not been clearly established. Serious unexpected adverse events (those not described in the approved product label or the investigators' brochure for investigational new drugs) require particular attention.

Information Sources

Information regarding adverse effects of medications is available from many sources and in multiple formats (i.e., print, CD-ROM, online). To assist in ADR detection, evaluation, and management, critical data regarding adverse reactions are needed (Table 3).

Table 3. Essential Elements for Characterizing ADRs

- Incidence and prevalence
- Mechanism and pathogenesis
- Clinical presentation and diagnosis
- Time course
- Dose relationship
- Reversibility
- Cross-reactivity/Cross-allergenicity
- Treatment and prognosis

FDA Safety Reports

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov.* In the message body enter: *subscribe medwatch* and your e-mail address.

This information may be gleaned from specialized ADR resources, texts, and other tertiary sources, including the FDA-approved product label. However, this information must often be augmented using additional data from secondary sources. At minimum, this should include searches of the bibliographic data bases from the National Library of Medicine (Medline and Toxline) and Excerpta Medica (Embase).

Primary reports describing adverse reactions and drug-induced diseases include spontaneous reports and other unpublished data available from the manufacturer or the FDA. All reports of adverse reactions reported to the FDA can be retrieved (without identifiers) under the legal authority of the Freedom of Information Act. Anecdotal and descriptive reports of ADRs (including case reports and case series) are occasionally reported in the literature but are often incomplete and inconclusive. Guidelines for evaluating adverse drug reaction reports have been described (56).

Observational studies, including case-control, cross-sectional, and cohort studies do not establish causality but can reveal associations of risk—the strength of which is measured by relative risk (cohort studies) or odds ratio. Design flaws and bias, however, occasionally render these studies altogether unreliable. Record-linkage studies using large prescription and medical data bases are increasingly being used to gather data regarding ADRs (56,59). Because they often include information from hundreds of thousands of patient records, well-designed linkage studies have the potential to generate robust epidemiological data. Prospective, randomized, controlled experimental studies (i.e., clinical trials) also can establish causality. These, along with well designed meta-analyses, are useful for identifying and quantifying certain types of adverse effects. Nonetheless, even these study designs have their limitations.

Calis KA, Young LR. Clinical analysis of adverse drug reactions. In: Atkinson AJ Jr, Daniels CE, Dedrick RL, Grudzinskas CV, Markey SP, editors.* Principles of Clinical Pharmacology. *San Diego: Academic Press; 2001. p. 319-32.